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PHENETHICILLIN

Phenethicillin (potassium alpha-phenoxyethyl penicillin), a new semi-synthetic oral penicillin, was first marketed by Beecham in England last year, and was subsequently introduced in the United States by Bristol as "Syncillin." Since the preliminary review of Syncillin in The Medical Letter (1: 97, Dec. 25, 1959), phenethicillin has become the most heavily promoted of current ethical drug products, with seven companies, in addition to Bristol, offering the antibiotic under as many different names: Alpen (Schering), Maxipen (Roerig), Ro-cillin (Rowell), Darcil (Wyeth), Chemipen (Squibb), Dramcillin-S (White), and Semopen (Massengill).

The general theme of the various companies' claims for phenethicillin is that the synthetic modification of the basic penicillin molecule in this product gives it important advantages over the older penicillins. The early claim that phenethicillin was less allergenic than other oral penicillins has been dropped; the principal claims now are that it produces much higher peak blood levels than oral penicillin V or even intramuscular potassium penicillin G, and that it has greater effectiveness than the older penicillins against many resistant staphylococcus strains.

LABORATORY STUDIES - Most of the comparisons of phenethicillin with the older penicillins have come from the laboratory and not from the clinic, and many of the studies support the manufacturers' claims. The findings and interpretations are, however, variable and conflicting, with results depending on the techniques used. The most comprehensive laboratory study is that of C. G. McCarthy and M. Finland (N. E. J. Med., 263: 315, Aug. 18, 1960). These investigators found serum concentrations of phenethicillin only slightly higher than those of penicillin V after equivalent doses given by mouth. They also found that peak serum concentrations achieved with phenethicillin were somewhat greater than with equivalent doses of potassium penicillin G given parenterally. The higher serum levels of phenethicillin were, however, of brief duration; the levels produced by intramuscular penicillin G were sustained much longer, with significantly greater total amounts recovered in the urine. Phenethicillin showed appreciably lower antibacterial activity than either V or parenteral G against test strains of hemolytic streptococci and pneumococci.

When tested in vitro with relatively low concentrations of some resistant strains of staphylococci, phenethicillin does appear to have an advantage over other oral penicillins, but this advantage is lost when the numbers of bacteria

approach those found in clinical staphylococcal lesions (R. W. Fairbrother and G. Taylor, Lancet, 2:400, Aug. 20, 1960; L. H. Geronimus, N. E. J. Med., 263:349, Aug. 18, 1960). The suggestion that phenethicillin or any other oral penicillin now available can be successfully used in any dosage to treat resistant staphylococcus infections is not supported by published studies.

CLINICAL STUDIES - In one recent clinical study (P. A. Bunn and R. Knight, Am. J. Med. Sci., 240:192, Aug. 1960), 25 patients with pneumococcal pneumonia were successfully treated with phenethicillin in doses of 250 or 500 mg. three times daily. But the authors conclude that when "...comparisons of efficacy are made among the many available penicillin products, no one of them has achieved such a superior position in management of patients with pneumonia that other preparations should be discarded." Oral potassium penicillin G and penicillin V in equivalent doses have, of course, been successfully used in the prophylaxis of rheumatic fever and in the treatment of infections (even with bacteremia) caused by streptococci, pneumococci, gonococci, and sensitive strains of staphylococci.

There is no doubt that phenethicillin is an effective oral penicillin. There is considerable doubt that in equivalent doses it is superior in clinical effectiveness to either oral or parenteral potassium penicillin G or to penicillin V. The superiority in absorption of phenethicillin and penicillin V provides no proved clinical advantage over buffered potassium penicillin G, particularly when the latter is taken on an empty stomach. With all of the oral penicillins, the recommended doses give serum levels which are more than adequate against penicillin-sensitive organisms. As McCarthy and Finland (cited above) point out, "...although the claim of better absorption and excretion and higher serum level of phenethicillin may be partly correct, strictly speaking, this is true in a very restricted sense and is therapeutically meaningless. Indeed, the claim is misleading since it clearly implies greater antibacterial and presumably curative activity, which, in fact, the drug does not possess...."

DOSAGE - In spite of the relative stability of both penicillin V and phenethicillin in gastric acid, the absorption of all three forms of oral penicillin is appreciably reduced by food; as a general rule, therefore, all oral penicillins should be taken on an empty stomach. Penicillin G appears to be less rapidly excreted than phenethicillin and penicillin V, but with all oral penicillins dosage every four to six hours is generally advisable, especially for the more severe infections. Equivalent doses of phenethicillin and penicillin V cost several times as much as penicillin G, and where cost is important there should seldom be occasion to prescribe either of the more expensive forms. In milder infections, buffered penicillin G in doses of 200,000 units (approximately equivalent to 125 mg. of phenethicillin or penicillin V) taken four times daily on an empty stomach is generally effective. In more severe infections such as pneumococcal pneumonia, this dose may be doubled.

No oral penicillin can be safely substituted for the large and frequent doses of parenteral crystalline penicillin G required in the treatment of pneumococcus or streptococcus meningitis or subacute or acute bacterial endocarditis. No oral penicillin has been accepted by public health authorities as a substitute for a paren-

teral penicillin in the treatment of syphilis; nor can any oral penicillin be a substitute for parenteral penicillin when the patient is vomiting, when there is disturbed gastrointestinal motility, or when the patient or family do not comprehend or cannot be relied upon to observe oral dosage schedules. Where regular ingestion of adequate amounts of oral penicillins according to directions can be assured, however, there is little justification for the use of parenteral penicillins for the treatment of routine infections, particularly in view of the greater risk of inducing penicillin hypersensitivity with parenteral penicillins.

COST - All of the oral penicillins are available in pediatric form, with penicillin G again much less expensive than the others. The following are approximate prices for buffered potassium penicillin G tablets and for one representative preparation of each of the other forms:

Penicillin G (200,000-unit tablet) - name brands	10¢ to 15¢
- other brands	5¢ to 10¢
Pen-Vee Oral (Wyeth) (125-mg. tablet)	40¢
Syncillin (Bristol) (125-mg. tablet)	40¢
Penicillin G pediatric (Pentids "400" syrup - Squibb) (200,000 units)	25¢
V-Cillin K pediatric (Lilly) (125 mg.)	40¢
Syncillin pediatric drops (Bristol) (125 mg.)	40¢

A NEW PENICILLIN FOR RESISTANT STAPHYLOCOCCI

A new synthetic penicillin which appears to be highly effective against resistant strains of staphylococci has been developed by the Beecham Research Laboratories in England and is the subject of a series of reports in the September 3rd issue of the British Medical Journal. The new penicillin, which is administered parenterally, is known in Britain as "Celbenin," and will be marketed in the United States by Bristol as "Staphcillin." No generic name has yet been assigned.

On the basis of preliminary laboratory and clinical studies this new penicillin appears to be unique among all penicillins in being highly resistant to staphylococcus penicillinase - the enzyme produced by resistant staphylococci which destroys other penicillins. The new penicillin shows variable activity against other bacteria, such as streptococci and pneumococci, and in general appears to have no advantages over older penicillins in the treatment of infections by other than resistant staphylococci.

Previous experience with other antibiotics indicates that strains of staphylococci resistant to this new penicillin will eventually emerge and will increase steadily in the hospital environment. Furthermore, the new penicillin is not free of the allergenic and superinfection potential of the older penicillins.

For these reasons it is to be hoped that this important new agent will not be used for routine bacterial infections for which older oral and parenteral penicillins are effective, but will be reserved exclusively for hospital use against severe, resistant staphylococcal infections.

HYGROTON

Chlorthalidone (Hygroton - Geigy) is a new oral diuretic of the sulfonamide group; its phthalimidine nucleus replaces the basic thiodiazine structure of the "thiazide" diuretics. Like some of its predecessors, Hygroton is claimed to give prolonged sodium excretion with minimum potassium excretion, to be effective where other diuretics have failed, and to have minimal side effects.

On the basis of present evidence, Hygroton appears to be an effective diuretic with very prolonged action (36 to 72 hours). There is no convincing evidence, however, that Hygroton is effective in patients who fail to respond to optimal dosage of the thiazides. The available data do suggest that less potassium loss occurs with Hygroton than with the thiazides, but significant loss of potassium may still occur, and suitable precautions must be taken to prevent depletion.

EFFECTS OF DOSAGE VARIATION - A comparison of different reports on the effects of varying doses of the drug shows some interesting discrepancies. M. Fuchs, et al. (Current Therapeutic Research, 2:11, 1960) gave Hygroton to ambulatory patients without salt restriction. These authors observed an average weight loss of only 0.5 lbs. with a dosage of 100 mg. daily for two days; increasing the dosage to 200 mg. resulted in a weight loss of 2.3 lbs. Their studies of sodium excretion in two hospitalized patients on each dosage showed corresponding and equally striking differences at the two dosage levels. Another study on ambulatory patients with well-controlled congestive heart failure (R. V. Ford, Texas State J. Med., 56:343, 1960) showed almost maximal loss of sodium with a 50-mg. dose, with no significant increase at 100 mg., and a decline in sodium loss at 200 mg. In these patients, whose sodium intake was restricted, nausea and weakness occurred at 100 mg. and were common at 200 mg. Other investigators did not observe such side effects with similar doses. These discrepancies point up the difficulty of testing diuretics and the care with which not only manufacturers' claims but also published reports must be scrutinized.

DOSAGE - In terms of clinical effectiveness, it has not been shown that the prolonged action of Hygroton offers any advantage. If further experience supports the claim that many patients can obtain adequate diuresis with a dose of 100 to 200 mg. or less taken three times a week, however, maintenance therapy may be less expensive for such patients with Hygroton than with other diuretics. The manufacturer recommends that 50 to 100 mg. of Hygroton be taken initially as a single morning dose, with subsequent dosage (given once a day or less frequently) individualized, but never more than 200 mg. in any day. Hygroton costs about 13¢ per 100-mg. tablet.

Serious side effects and toxicity have not yet been reported, but as with all new drugs, the possibility that such effects will appear with longer experience cannot be ruled out. Whether Hygroton will prove more or less sensitizing than the thiazides remains to be seen; the long action of the drug would be a disadvantage if serious sensitizing effects do occur. Pending more extensive clinical trial, Hygroton can only be accorded a place as another potent oral diuretic which may prove to be a useful alternative to the thiazide diuretics for some patients.

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